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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
GAMBEL, PHILLIP	

ART UNIT	PAPER NUMBER
1644	10

DATE MAILED: 10/11/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/758173	Applicant(s) ANDERSON
	Examiner GEMBEL	Art Unit 1644

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☑ Responsive to communication(s) filed on _____

2a)☐ This action is **FINAL**. 2b)☑ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☑ Claim(s) _____ is/are pending in the application. 21-36

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☑ Claim(s) _____ is/are rejected. 21-36

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☑ The drawing(s) filed on _____ is/are: a)☑ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a)☑ The translation of the foreign language provisional application has been received.

15)☑ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☑ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____.
4) ☐ Interview Summary (PTO-413) Paper No(s). ____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Applicant's amendment, filed 4/12/02 (Paper No. 4), has been entered.
Claims 32-36 have been added.
Claim 30 has been amended.

Applicant's election without traverse of the administration of anti-B7.1 antibody in Paper No. 4, filed 4/12/02, is acknowledged.

Claims 21-36 are pending and being acted upon as they read on the election invention of administering anti-B7.1 antibodies to treat B cell lymphoma.

Claims 1-20 have been canceled previously.

2. No Information Disclosure Statement has been filed with this application.

3. Applicant should amend the first line of the specification to update the status of the priority documents. For example, USSN 08/487,550 is now U.S. Patent No. 6,113,898.

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

5. The Abstract of the Disclosure is objected to because it does not adequately describe the claimed invention. Correction is required. See MPEP 608.01(b).

6. Formal drawings, filed 1/12/01, have been submitted which comply with 37 CFR 1.84.

7. The application is required to be reviewed and all spelling, TRADEMARKS, and like errors corrected.

Trademarks should be capitalized or accompanied by the ™ or ® symbol wherever they appear and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the trademarks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Appropriate corrections are required

8. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 21-(25)-36 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Page 34, paragraph 2 of the instant specification discloses that "one skilled in the art would be able, by routine experimentation, to determine what an effective amount of anti-B7 antibody would be for the purpose of treating carcinogenic tumors"

In vitro and animal model studies have not correlated well with in vivo clinical trial results in patients. Since the therapeutic indices of immunotherapeutic regimens can be species- and model-dependent, it is not clear that reliance on the ability of B7-1-specific antibodies to block B7-mediated accurately reflects the relative ability of the claimed invention to treat B cell lymphomas with B7-1-specific antibodies that do not kill (or deplete) B cell lymphomas.

Pharmaceutical therapies in the absence of in vivo clinical data are unpredictable for the following reasons; (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has not effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

It has been known that the response of animals to immunotherapy has not been predictable as that of the response to chemotherapy. Furthermore, it does not appear that applicant has provided either in vitro or in vivo experimental results. It is noted that even experimental results relying upon cell lines adapted for culture in vitro do not necessarily reflect the therapeutic barriers presented by neoplastic cells in a clinical setting. For example, Dermer states that the widely disparate character of human tumor cell lines contributes greatly to chemotherapy's continued ineffectiveness against cancer (Biotechnology 12: 320, 1994).

Dillman further states that there are no unconjugated monoclonal antibodies that have proven therapeutic benefit in hematologic malignancies or solid tumors (J. Clin. Oncol., 1994; see entire document, particularly the Abstract's Conclusion). Therefore, it is unclear that unconjugated B7-1-specific antibodies or non-depleting B7-1-specific antibodies could be effective against B cell lymphoma.

It is noted that instant claim 25 recites "a depleting antibody", however it is unclear in the absence of objective evidence that "a depleting antibody" rather than an antibody conjugated to a cytotoxic agent (e.g. radionuclide or toxin) would be able to treat B cell lymphoma, encompassed by the claimed invention.

Falini et al. (Lancet 339: 1195-1196, 1992) disclose that the anti-CD30 Ber-H2 antibody which binds Hodgkin and Reed-Sternberg cells, has no anti-tumor effects, therefore for clinical use such antibodies have to coupled to cytotoxic agents (see entire document, including page 1195, column 1).

Tumor heterogeneity and hardiness as well as the selection of the appropriate therapeutic strategy remain major barriers to B7-specific immunotherapy of tumors. The specification does not teach how to extrapolate data obtained from in vitro experimental observations to the development of effective in vivo human therapeutic methods for treating B cell lymphoma where the B7-specific antibodies are not conjugated to a cytotoxic agent, particularly where the B7-specific antibodies are non-depleting.

In addition, it is not clear whether unconjugated depleting B7 antibodies can inhibit B cell lymphomas. It does not appear that the specification discloses conjugated B7-specific antibodies.

In view of the lack of predictability of the art to which the invention pertains the lack of established clinical protocols for effective therapies of inhibiting B cell lymphomas with unconjugated antibodies, undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods to treat B cell lymphomas with B7-specific antibodies, commensurate in scope with the claimed invention.

10. Claim 24 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 24 is indefinite in the recitation of "16C10, 7C10, 20C9 and 7B6" because their characteristics are not known. The use of "16C10, 7C10, 20C9 and 7B6" monoclonal antibodies as the sole means of identifying the claimed antibodies renders the claim indefinite because "16C10, 7C10, 20C9 and 7B6" are merely laboratory designations which do not clearly define the claimed products, since different laboratories may use the same laboratory designations to define completely distinct hybridomas / cell lines.

Applicant should amend the claims to recite the appropriate SEQ ID NOS., as recited in claim 32 to obviate this rejection.

Applicant should specifically point out the support for any amendments made to the disclosure. See MPEP 714.02 and 2163.06

With respect issues under 35 USC 112, first paragraph, enablement with respect to the deposit of biological materials, it is noted that the sequence of an entire immunoglobulin satisfies the biological deposit of said immunoglobulin. Note that satisfaction for the biological deposit of the specific 16C10, 7C10, 20C9 and 7B6 antibodies require the disclosure and recitation of its entire amino acid sequences and not based upon partial sequences.

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 21-23, 25, 27-31, 33-36 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Imam et al. (U.S. Patent No. 5,304,635) in view of Delabie et al. (Blood 82: 2845-2852, 1993) AND/OR Munro et al. (Blood 83: 793-798, 1994), Falini et al. (Lancet 339: 1195-1196, 1992) and the well known generation of recombinant antibodies, including primatized antibodies and dosing known to the skilled artisan at the time the invention was made as acknowledged by pages 13-16 and 21-39 of the instant specification.

Imam et al. teach the use of a growth inhibiting amount of a B-cell specific antibodies, including radioimmunotherapy, to treat B cell lymphoma's such as Hodgkin's lymphoma (see entire documents, including Background of the Invention, including column 3, lines 11-12 and column 4; Summary of the Invention, including column 5, lines 35-40; Detailed Description of the Invention, including columns 9-10, overlapping paragraph).

Imam et al. differs from the claimed methods by not disclosing the that the B cell antigen target of B cell lymphomas was B7-1.

Delabie et al. (Blood 82: 2845-2852, 1993) teach the B7/BB1 molecule (B7-1) was expressed on Reed-Sternberg cells in Hodgkin's Disease and contributes to the Hodgkin's syndrome (see entire document, including Abstract). Delabie et al. also teach that B7/BB1 was also expressed on subpopulations of neoplastic Cells of follicular lymphomas and anaplastic large-cell lymphoma (see Discussion, including page 2851, column 1). Delabie et al. also discuss that cell-mediated cytotoxic killing of Reed-Sternberg cells might explain the relative indolent clinical behavior of most subtypes of Hodgkin's disease (page 2851, column 1, paragraph 2).

Munro et al. (Blood 83: 793-798, 1994) teach the in vivo expression of B7 by benign transformed germinal center B cells and B cells of follicular lymphomas (see entire document, including the Abstract and Discussion). Also, Munro et al. teach that the majority of Reed-Sternberg cells or malignant mononuclear variants, which potentially contributes to the lymphocytic accumulation that is a feature of Hodgkin's disease (see entire document, including Abstract and Discussion).

Falini et al. teach the use of immunotoxin to treat Hodgkin's disease, providing an expectation of success in treating B cell lymphomas with antibodies that bind Hodgkin and Reed-Sternberg cells (see entire document, including Abstract). Falini et al. also note manipulating dosing and timing of administration to increase efficacy (see page 1196, column 2, paragraph 1). Further, Falini et al. note that the use of chimeric or humanized antibodies would circumvent the problems associated with repeated dosing (see page 1196, column 2, paragraph 1), thereby providing further motivation and expectation of success in applying the well known and practiced use of recombinant antibodies for human therapy.

In support, pages 13-16 and 21-39 of the instant specification acknowledge the well known generation of recombinant antibodies, including primatized antibodies and the antibodies comprising different human gamma chains constant regions for human therapy at the time the invention was made. Further, the specification also acknowledges the amount of an antibody useful to produce a therapeutic effect can be determined by standard techniques well known to those of ordinary skill in the art (e.g., see page 32, paragraph 2 and page 34, paragraph 2).

Given the experience by the ordinary artisan in the art at the time the invention was made, as taught by Falini et al. And acknowledged by the specification as filed, the claimed dosing and modes of administration would have been known and practiced by the ordinary artisan at the time the invention was made in achieving the therapeutic endpoint of treating B cell lymphomas.

Therefore, one of ordinary skill in the art would have been motivated to treat B cell lymphomas with B7-1-specific antibodies, particularly B7-1-specific antibodies conjugated to a cytotoxic agent, given the teachings of the prior art teachings that anti-B cell antibody conjugates treat B cell lymphomas and that anti-B7-1 antibodies bind B cell lymphomas at the time the invention was made. Further, the priori art provides motivation to treat B cell lymphomas by targeting Reed-Sternberg cells, which contribute to the clinical manifestations of Hodgkin's Disease.

From the teachings of the references, it was apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

13. No claim is allowed.

It is noted that the specific B7-1-specific antibodies recited in claims 24 and 32 are deemed free of the prior art.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014.

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